A multicenter, collaborative, non-blinded, randomized controlled trial to examine the effectiveness of favipiravir plus camostat mesilate and inhaled ciclesonide combination therapy to control aggravation of novel coronavirus infection-related pneumonia

Statistical Analysis Plan ver2.1

Revision history

SAP Ver.	Protocol Ver.	Creation/ revision date	Author	Details
1.0	2.0	November 5, 2020	Takuya Kawahara	Development of first version
2.0	5.0	May 28, 2021	Takuya Kawahara	Revision
2.1	5.0	July 12, 2021	Takuya Kawahara	Revision

Contents

1. Statistical analysis plan definition

The purpose of this plan is to describe the details of statistical analysis in the multicenter, collaborative, non-blinded, randomized controlled trial to examine the effectiveness of favipiravir plus camostat mesilate and inhaled ciclesonide combination therapy to control aggravation of novel coronavirus infection (COVID-19)-related pneumonia' (this study hereafter).

2. Study outline

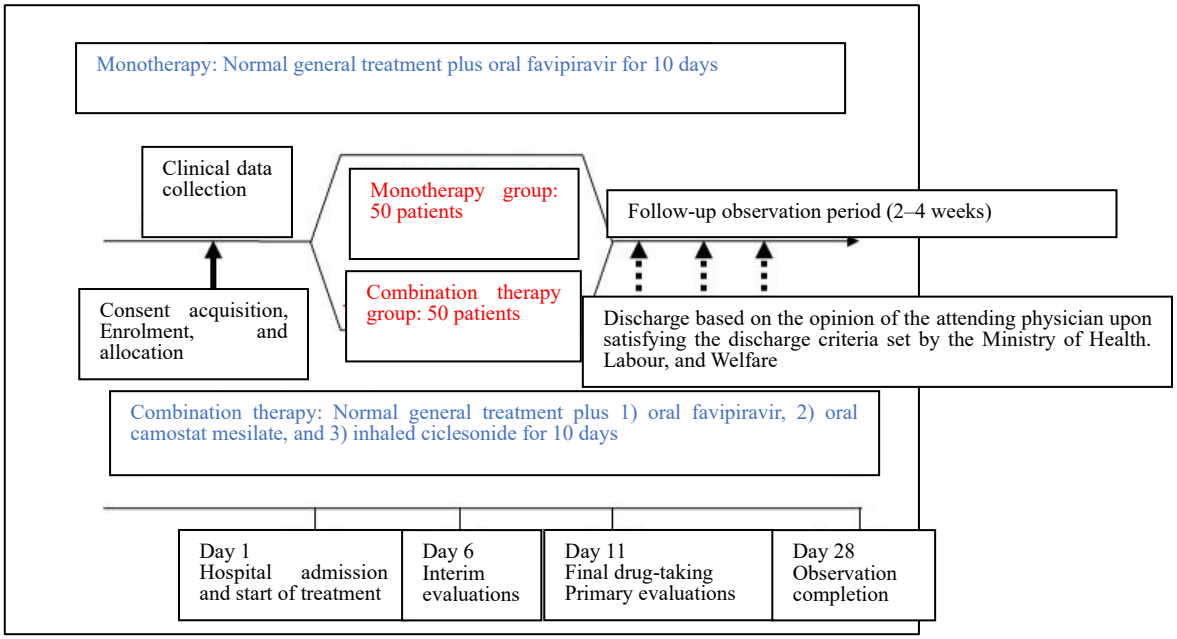
2.1. Objectives

In patients with COVID-19-related pneumonia divided into a group given a single agent (favipiravir) and a group given combination therapy of favipiravir plus camostat mesilate and inhaled ciclesonide, we aim to compare the period until discharge from the hospital between the two groups and examine the safety of combination therapy. Furthermore, the incidence of adverse events will be compared between the two groups to compare the safety of combination therapy.

2.2. Study design and plan

1. Type of study

Randomized comparative, non-blinded, actual drug (treatment) controlled, parallel group comparison, treatment



2. Study outline

Figure: Study flow chart (as mentioned in section 2.10, the study has been revised to include 59 patients in each group)

2.3. Inclusion criteria

Inclusion criteria: To participate in this study, all of the following criteria must be satisfied.

1) Patients who have given written consent to participate in the study
2) Patients aged ≥20 years at the time of consent, regardless of sex
3) SARS-CoV-2 PCR or LAMP test-positive individuals or individuals with COVID-19

confirmed using other diagnostic tests detailed by the Ministry of Health, Labour and Welfare (MHLW)

4) Patients with clear COVID-19-related pneumonia confirmed based on chest computed tomography (CT) scan
5) Patients who are able to be hospitalized during the study treatment (10 days)
6) Patients who are able to inhale ciclesonide using an inhaler
7) In the event of female patients who are premenopausal and those with confirmed negative pregnancy test before administration of the investigational drug

2.4. Exclusion criteria

When any of the following criteria are applicable, participation in this study will not be allowed.

1) Patients who have received systemic administration of drugs with suggested antiviral inhibitory action against SARS-CoV2 within 28 days before providing consent
2) Patients with relapse or repeat infection with SARS-CoV2
3) Patients with concurrent respiratory infection other than COVID-19 (such as chronic infection, acid-fast bacteriosis, and mycosis)
4) Patients suspected of having concurrent congestive heart failure
5) Patients with severe hepatic impairment corresponding to Child-Pugh classification C
6) Patients with renal impairment requiring dialysis
7) Patients suspected of having immunodeficiency such as patients with HIV
8) Patients with consciousness disturbance such as disorientation
9) Patients using immunosuppressants
10) Patients using inhaled or oral steroids
11) Patients who are pregnant or who might be pregnant
12) Female patients who do not consent to using the birth control pill; mechanical contraceptive devices, such as intrauterine devices; barrier methods (diaphragm, condom); or a combination of such methods from the start of favipiravir administration until 90 days after completion
13) Male patients with a partner who does not consent to contraception using the contraception methods listed above (12)
14) Patients with hereditary xanthinuria
15) Patients with diagnosis of hypouricemia (<1 mg/dL) or xanthine urolithiasis.
16) Patients with poorly controlled gout or hyperuricemia
17) Patients with a history of hypersensitivity to favipiravir, camostat mesilate, or ciclesonide
18) Severe patients in the intensive care unit (ICU) requiring artificial ventilation or extracorporeal membrane oxygenation (ECMO)

19) Patients who are judged by the principal investigator or subinvestigator to be inappropriate for inclusion in the study

2.5. Efficacy endpoints

1. Primary endpoint

Hospitalization duration: The period from hospital admission until satisfying the discharge criteria.

2. Secondary endpoints

(1) Changes in clinical findings: Body temperature, oxygen usage status, respiratory rate, oxygen saturation, severity, presence or absence of artificial ventilator usage, ECMO usage, presence or absence of ICU management, and state of other concurrent drug usage

(2) Changes in laboratory test findings: Alb, lymphocyte count, CRP, D-dimer, PIC, TAT, white blood cell count, thrombocyte count, bilirubin, AST, ALT, LDH, ALP, CK, creatinine, BUN, Na, K, Glu, uric acid, procalcitonin

(3) Genome size of SARS–CoV2

(4) Presence or absence of antibody (IgM and IgG) production

3. Exploratory endpoints

Scored severity, SpO_2, evaluation of changes on chest CT

Evaluation method (scoring)

Severity (evaluation on days 4, 8, 11, 15, and 29 compared with at hospitalization)

Improvement of 2 grades: +2 points

Improvement of 1 grade: +1 point

No change: 0 points

Deterioration of 1 grade: -3 points

Deterioration of 2 grades: -5 points

Regarding severity, the criteria of the Novel coronavirus Infection Medical Practice Guideline guide version 3.0 will be used.

Severity	Oxygen saturation	Clinical status	Medical treatment points
Mild	$SpO_2 \geq 96\%$	Without respiratory symptoms, Cough only, no shortness of breath	-Symptoms often spontaneously improve, but in some instances rapidly progress -Patients with risk factors should be hospitalized
Moderate I Without	$93\% < SpO_2 < 96\%$	Shortness of breath, findings of pneumonia	-Careful observation after hospitalization -Even if hypoxemia is noted, some patients do not complain of respiratory distress

respiratory failure			-It is important to treat patient anxiety also
Moderate II With respiratory failure	$SpO_2 \leq 93\%$	Requiring oxygen therapy	-Determine cause of respiratory failure -Consider transfer to an institution capable of providing advanced medical care -Avoid high flow nasal oxygen, and CPAP as much as possible and control aerosol generation
Severe		ICU admission or artificial ventilation needed	-2 types of severe pneumonia based on artificial ventilation management (type L, and type H) -Type L: soft lungs, with increased ventilatory volume -Type H: Pulmonary edema, consider introduction of ECMO -It is difficult to determine the transition from type L to type H

Evaluation of SpO2 changes

$SpO_2 \geq 96\%$ in room air: 0 points

$93\% \leq SpO_2 < 96\%$ in room air: -1 point

$90\% \leq SpO_2 < 93\%$ in room air: -2 points

$SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 1–2 L/min: -3 points

$SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 3–4 L/min: -4 points

Oxygen therapy with a mask, reservoir bag: -5 points

Noninvasive positive pressure ventilation, high flow nasal oxygen: -6 points

Artificial ventilation, ECMO: -7 points

Evaluation of pneumonia based on chest CT

Marked improvement: +2 points

Slight improvement: +1 point

No change: 0 points

Slight exacerbation: -3 points

Marked exacerbation: -5 points

2.6. Safety endpoints

Incidence of adverse events

Incidence of adverse events, including abnormal changes in vital signs, laboratory test values, and physiological function tests

2.7. Discontinuation criteria for the overall clinical trial

The overall study will be discontinued in the event of any of the following. When the principal investigator discontinues the study, they will notify study subjects of the discontinuation immediately,

then provide appropriate medical care, and adopt other necessary measures. Once the principal investigator has discontinued the study, they will report the discontinuation, reason for discontinuation, and summary of results in writing to the hospital directors without delay.

1) When matters regarding the quality, effectiveness, and safety of the investigational drug; important information that might affect the implementation, or continuation of the study; and other important information for the proper implementation of the study are discovered.
2) When inclusion of study subjects is difficult and it is judged difficult to reach the planned number of subjects.
3) When the study objectives are achieved before reaching the planned number of subjects or before completing the planned period.
4) When a revision of the protocol is instructed based on the opinion of the certified clinical research review board, which is difficult to adopt.
5) When the certified clinical research review board determines that study should be discontinued.
6) When a serious or ongoing violation has occurred resulting in the breach of the Clinical Trials Act, ordinance for enforcement, or this protocol.

2.8. Discontinuation criteria for each individual subject

When the principal investigator or subinvestigator judges that the following changes in the medical status of a subject means that the subject concerned can no longer participate in this clinical trial owing to safety reasons and when a subject or their legal representative requests to withdraw participation from the study, participation of the subject must be discontinued at any time during the study period.

1) When it is deemed difficult to continue the study owing to the onset of illness and the like
2) When a subject can no longer be followed-up
3) When pregnancy or suspected pregnancy occurs
4) When a subject or their legal representative requests to withdraw participation from the study
5) Non-compliance in taking the drugs
6) Violation of protocol
7) When contraindicated drugs must be administered or when they have been administered
8) When a caregiver who can cooperate in the study is no longer available
9) When, for other reasons, the principal investigator or subinvestigator judges the study continuation to be difficult

2.9. Study implementation period

November 11, 2020 to September 30, 2021

2.10. Setting the number of subjects

Target number of subjects: 118 patients (normal treatment group: 59 patients, combination therapy group: 59 patients)

Grounds for setting the number of subjects

In report 10 analyzing the clinical course of 1,099 patients with COVID-19 in the Chugoku region of Japan, the median length of hospitalization was 12.0 days. On the other hand, in 26 patients with COVID-19-related pneumonia who received additional treatment as inpatients of the International University of Health and Welfare Narita Hospital, the median length of hospitalization was 18.0 days. This difference is thought to involve the difference in the number of patients and discharge criteria as well as severity and the presence or absence of concurrent pneumonia. In the present study, the subject sample included patients with concurrent pneumonia corresponding to moderate or more severe illness, and considering that both groups use favipiravir, the median length of hospitalization in the monotherapy group was assumed to be 15.0 days.

Furthermore, regarding the therapeutic effects, although clinical trials and investigations of the effectiveness of each drug are underway, there are no reports on the effects of the combination therapy of favipiravir plus camostat mesilate as well as inhaled ciclesonide used in the present study. However, with regard to inhaled ciclesonide (single agent), the “study of the effects of ciclesonide usage for COVID-19: retrospective cohort study” led by the Japanese Association for Infectious Diseases has been underway, and the “multicenter, collaborative, non-blind RCT to examine the effectiveness and safety of inhaled ciclesonide for patients with asymptomatic or mild COVID-19 (jRCT: CRB3180024)” led by the National center for Global health and Medicine has been underway, and the results are anticipated. Furthermore, a specific clinical trial (jRCT: CRB3180024) led by the University of Tokyo Hospital has been underway with regard to combination therapy of nafamostat (injection) with favipiravir, which is said to have the same effect as camostat mesilate (oral agent), whereas Ono Pharmaceutical Co., Ltd is planning a clinical trial, and the outcomes of these studies among others are anticipated. Therefore, it is expected that inhaled ciclesonide and camostat mesilate might both be effective for the control of COVID-19 through different mechanisms, and thus, it was assumed that the median length of hospitalization with combination therapy would be shorter at 2.22 days than favipiravir monotherapy (the median length of hospitalization is assumed to reduce to 12.78 days).

In both groups, exponential distribution in the length of hospitalization was assumed. One of the discharge criteria of the MHLW includes 10 days having passed since onset. This leads us to assume that many patients do not satisfy the discharge criteria within 10 days. Therefore, in setting the number of patients, 10 days were subtracted from the median length of hospitalization of 15 days in the

monotherapy group to obtain 5 days and 10 days were subtracted from the median length of hospitalization of 12.78 days in the combination therapy group to obtain 2.78 days (hazard ratio: 1.8). When two-sided significance level was set to 5% and the follow-up period was 35 days (based on the experience of the International University of Health and Welfare), the maximum follow-up duration of each individual patient was 35 days. Taking into consideration the discharge criteria of the MHLW, 10 days were subtracted, and to set the number of patients, 25 days was used, and the enrolment period was 0 days (irrespective of the enrolment time, the maximum follow-up period was approximately 35 days, and therefore, in setting the number of cases, the enrolment period was defined as 0 days); to detect an intergroup difference with a statistical power of 80%, a total of 98 patients were needed for the two groups (number of expected events: 97). Considering that approximately 16% of the patients will withdraw their participation, the target number of patients was set at 118 (59 patients in the monotherapy group and 59 patients in the combination therapy group).

Furthermore, when 98–99 events were confirmed in an analysis set of 100 patients, assuming that the median period until discharge in the combination therapy group is reduced to 2.00 days (hazard ratio: 1.67), statistical power of 70% can be ensured.

2.11. Provisions regarding concomitant drugs (therapies)

・Prohibited concomitant drugs

During the study implementation period (from consent acquisition until the day of the final observation), use of the following contraindicated drugs is forbidden.

1) Oral and injected systemic adrenocorticosteroids
2) Inhaled steroids other than inhaled Alvesco
3) Drugs that might have a therapeutic effect on COVID-19 (such as lopinavir-ritonavir combination agent, chloroquine, hydroxychloroquine, tocilizumab, and nafamostat)

・Concomitant drugs that require attention

Regarding the following drugs, there is the possibility of drug interaction; therefore, concurrent use with favipiravir requires attention. Furthermore, favipiravir is not metabolized by cytochrome P-450 (CYP), but by aldehyde oxidase (AO), and in part by xanthine oxidase. Favipiravir inhibits AO, and CYP2C8; however, a CYP induction effect has not been observed to date.

1) Pyrazinamide
2) Repaglinide
3) Theophylline
4) Famciclovir
5) Sulindac

Permissible concomitant drugs and permissible therapies are not set.

2.12. Allocation

- Allocation method: Stratified block randomization (allocation ratio 1:1)
- Allocation adjustment factors: Age (≥50 and ≤50 years), sex, severity, the presence or absence of complications (with any or none of the following complications: diabetes mellitus, ischemic heart disease, and chronic respiratory illness)

The allocation results will be presented via electronic data capture (EDC) by inputting and checking the necessary matters such as allocation adjustment factors in the EDC system. The principal investigator or subinvestigator will contact the study secretariat and confirm the allocation results at the time point when study consent has been provided. The principal investigator or subinvestigator will commence treatment in accordance with the allocation results and initiate the study. Furthermore, a study ID specific to this study will be issued to study subjects upon enrolment, and thus the principal investigator will create a correspondence table, which they will safely kept in an appropriate manner.

3. Observations, tests, and examination items

3.1. Study schedule

Item	Evaluation time	Day	Admission day	0 weeks	After 3 days of treatment (±1 day)*	After 7 days of treatment (±1 day)*	After 10 days of treatment (±1 day)*	After 2 weeks of treatment (±2 days)*	At completion (discontinuation) after 4 weeks (±3 days)*
	Dose start date			10-day Treatment period				Post observation period*	
			Day0	Day1	Day4	Day8	Day11		
Consent acquisition			○						
Verification of subject background			○						
Investigational drug administration				←	—	—	→		
Subjective symptoms, and objective findings			○	○	●	●	●	●#※	●$
Observation of adverse events				←	—	—	—	→	●$
Measurement of body temperature and SpO2			○	○	●	●	●	●#※	●$
Recording of oxygen flow rate used			○	○	●	●	●	●#※	●$
Laboratory tests	Blood tests		○	○	●	●	●	●#※	●$
	Blood biochemistry			○	●	●	●	●#※	●$
	Blood coagulation test			○		●		●#※	●$
	SARS－CoV2 PCR		○	○		●		●#※	●$
	Antibody test			○		●		●#※	●$
Chest X-ray			○		●	●	●	●#※	●$
Chest CT			○			●		●#※	●$

The symbols are as follows: ○ Item evaluated once before commencement of administration of the investigational drug (either day 0 or day 1); ● Item performed after the start of administration of the investigational drug; ＃: when symptoms improve and the subject is discharged before day 15, the results from day 11 can be used; $ Evaluations on day 29 are limited to patients who could be examined in an out-patient basis after discharge. *When it is difficult to perform tests and evaluations owing to circumstances of the hospital (for reasons such as Sunday, public holiday, or doctor's no consultation day), it is possible to change the set date within the range of ±1–3 days.*When hospitalization is continued, the same tests are to be repeated each week.

3.2. Observation and test items

1) Medical examination (subject background, etc. day 0 or 1)

Physical findings will be observed by visual examination, palpation, auscultation, and percussion test, etc.

Furthermore, the following items will be examined to check the subject's background.

Sex, date of birth (age), race, body height, weight, smoking (presence or absence of habit, number of cigarettes, and number of years of smoking), history of present illness, medical history, complications, drug-taking history, drug allergies, date of COVID-19 onset (date of PCR test

positivity), presence or absence of pregnancy, the desire for and possibility of pregnancy, presence or absence of breast-feeding, level of consciousness, treatment status before hospitalization, state of physical activity, and COVID-19 severity assessment

2) Vital signs, etc. (day 0 or 1, 4, 8, 11, 15, 29)

Body temperature, blood pressure (BP), heart rate, SpO_2, state of oxygen usage, respiratory rate

3) Blood test [Day 0 or 1 (before study commencement), 4, 8, 11, 15, 29 (or at study completion)]

Hematology test: WBC (neu, mono, lympho, eosino, baso), RBC, Hb, Ht, Plt

Coagulation function: PT/INR, APTT

Blood biochemistry: AST, ALT, LD, ALP, γGTP, T-Bil, TP, Alb, BUN, Cre, eGFR, UA, TG, T-cho, HDL-C, LDL-C, Na, K, Cl, Ca, Glu

Immunology test: COVID-19 antibodies

The following measurements are taken on day 0 or 1 only: HbA1c, CK, procalcitonin, ferritin, KL-6, BNP (or NT-proBNP), D-dimer, PIC/TAT, IL-6 [in the event of abnormally high values, follow-up changes over time at the discretion of the principal investigator, or subinvestigator (except for HbA1c)]

4) Imaging procedures

• Chest X-ray (day 0 or 1, 4, 8, 11, 15, 29)

• HRCT Day 0 or 1, 8, 15, 29（or at study completion)

(In addition to the above, blood tests, imaging procedures, and physiological tests will be performed as needed when symptom exacerbation is suspected)

4. Study endpoints

4.1. Primary endpoint

Length of hospitalization: The period from hospitalization until meeting the discharge criteria

The period from hospitalization until discharge: The number of days after hospitalization until the clinician judges discharge to be possible when an improvement is observed in the clinical symptoms of pneumonia, chest imaging findings, and oxygen demand as a result of treatment and when the discharge criteria of the MHLW are satisfied. If discharge is not possible owing to social circumstances, the number of days until the above-mentioned discharge criteria are satisfied will be used instead.

Grounds for setting the primary endpoint

It has been found that patients with COVID-19 present relatively varied symptoms, including fever, cough, sputum, smell and taste disturbance, diarrhea, and headache; however, it has been found that the degree of symptoms differ depending on the time of onset and time of hospitalization, and in the present clinical trial, to evaluate the patients' level of improvement in pneumonia, we defined the length of hospitalization as the primary endpoint. For SARS-CoV-2, from the perspective of the sensitivity and specificity, the PCR test was not used as it was judged that a bias could not be avoided. Furthermore, with regard to fever, many patients do not present fever at the time of hospitalization, and therefore, it was judged unsuitable as an indicator of improvement, and thus not adopted. Regarding the improvement in findings on chest imaging and oxygen demand, with the length of hospitalization included as the primary endpoint, other items were set as the secondary and exploratory endpoints.

4.2. Secondary endpoints

(1) Changes in clinical findings: Body temperature, oxygen usage status, respiratory rate, oxygen saturation, severity, presence or absence of artificial ventilator usage, ECMO usage, presence or absence of ICU management, and state of other concurrent drug usage
(2) Changes in laboratory test findings: Alb, lymphocyte count, CRP, D-dimer, PIC, TAT, white blood cell count, thrombocyte count, bilirubin, AST, ALT, LDH, ALP, CK, creatinine, BUN, Na, K, Glu, uric acid, procalcitonin
(3) SARS–CoV2 viral genome size (days 8, 15, and 29 only)
(4) Presence or absence of antibody (IgM and IgG) production (days 8, 15, and 29 only)

4.3. Exploratory endpoints

Scored severity, SpO_2, evaluation of changes on chest CT

Evaluation method (scoring)

Severity (evaluation on day 4, 8, 11, 15, and 29 compared with at hospitalization)

Improvement of 2 grades: + 2 points

Improvement of 1 grade: + 1 point

No change: 0 points

Deterioration of 1 grade: -3 points

Deterioration of 2 grades: -5 points

Evaluation of SpO_2 changes (evaluation on day 4, 8, 11, 15, and 29 compared with at hospitalization)

$SpO_2 \geq 96\%$ in room air: 0 points

$93\% \leq SpO_2 < 96\%$ in room air: -1 point

$90\% \leq SpO_2 < 93\%$ in room air: -2 points

$SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 1–2 L/min: -3 points

$SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 3–4 L/min: -4 points

Oxygen therapy with a mask, reservoir bag: -5 points

Noninvasive positive pressure ventilation, high flow nasal oxygen: -6 points

Artificial ventilation, ECMO: -7 points

Evaluation of pneumonia based on chest CT (evaluation on day 8, 15, and 29 compared with at hospitalization)

Marked improvement: +2 points

Slight improvement: +1 point

No change: 0 points

Slight exacerbation: -3 points

Marked exacerbation: -5 points

4.4 Safety endpoints

Incidence of adverse events

Incidence of adverse events, including abnormal changes in vital signs, laboratory test values, and physiological function tests

5. General matters for statistical analysis

5.1. Presentation of summary statistics and values

(1) In the summary statistics for continuous variables, we calculated the number of patients, mean value, standard deviation, minimum value, 25th percentile, median, 75th percentile, and the maximum value. The significant digit for the mean value, standard deviation, 25th percentile,

median, and 75th percentile is as the significant digit of each individual data +1. For example, if the effective digit for individual data of a certain variable is one decimal place, then the significant digit for the mean value, standard deviation, and median would be +2. However, the significant figure for the minimum value and maximum value would be the same as each individual datum. However, when data includes digits of a number that is clearly greater than the true significant digit, such as measurements obtained from an instrument, then the mean, standard deviation, and median will be presented to 3 decimal places, whereas the maximum value and minimum value will be presented to 2 decimal places.

(2) Summary statistics for discrete variables will include the number of evaluated patients and ratio. The number of patients will be presented as an integer value. The ratio will be presented as a percentage, rounded off to 2 decimal places, and presented with 1 decimal place.

(3) Values obtained in the analysis results, such as the minimum mean-square value, and related confidence interval (CI), will be rounded off to 4 decimal places, and presented with 3 decimal places.

(4) When the P value is <0.001, it will be presented as <0.001. When it is >0.001, it will be rounded off to 4 decimal places and presented as a digit up to 3 decimal places.

(5) Unless otherwise specified, the significance level of the tests will be 5% bilaterally. Missing data will not be supplemented.

5.2. Software used

The software used for analyses, tabulations, and some chart output will be SAS version 9.4 (SAS Institute Inc.). For simple gross tabulations, such as to calculate total values and ratios, Microsoft Excel will be used in some instances.

6. Data handling

6.1. Handling of baseline data

For the baseline values of each variable, the measurements obtained at the following time points will be used.

・ The day of hospitalization (Day 0) or the day of the start of treatment (day 1)

Subjective symptoms, objective findings, body temperature, SpO_2, oxygen flow rate used, hematological test, blood biochemistry, blood coagulation test, antibody test, chest X-ray, chest CT

However, when measurements are taken several times on day 0 or day 1 before the start of treatment, day 0 will be used in priority as the baseline value.

6.2. Data handling

1. Permissible range

As a rule, data within the permissible range stipulated in section “3.1 Study schedule” will be used in the analyses.

6.3. Calculation of derived variables

1. Severity

Severity will be classified into mild, moderate I, moderate II, and severe.

Mild:	$SpO_2 \geq 96\%$
Moderate I:	$93\% < SpO_2 < 96\%$
Moderate II:	$SpO_2 \leq 93\%$
Severity:	The patient is admitted to the ICU (evaluated during the period from the day of admission until the day of discharge from the ICU) or the SpO_2 measurement conditions are “under artificial ventilation management” (irrespective of the SpO_2 value)

2. Scored severity

Severity in section 1. is stipulated according to 4 stages; however, scored changes from baseline using the following method will be defined as scored severity.

Improvement of 2 grades: +2 points

Improvement of 1 grade: +1 point

No change: 0 points

Deterioration of 1 grade: -3 points

Deterioration of 2 grades: -5 points

3. Scored respiratory function (secondary endpoint: evaluation of changes in SpO_2)

A score will be assigned according to the SpO_2 value and measurement conditions (1) at baseline, and (2) on each evaluation day. The value obtained by subtracting score (1) from score (2) will be defined as the change in respiratory function score for each evaluation day.

The algorithm for assigning scores is as follows:

When the O_2 administration route is inhalation in room air:

$SpO_2 \geq 96\%$ in room air: 0 points

$93\% \leq SpO_2 < 96\%$ in room air: -1 point

$90\% \leq SpO_2 < 93\%$ in room air: -2 points

When the oxygen administration route is O_2 administration:

O2 administration route via cannula

When O_2 administration rate is 2 L/min (FiO_2 0.28), $SpO_2 \geq 90\%$: -3 points

When the O_2 administration rate is >2 L/min (FiO_2 0.28) and <4 L/min (FiO_2 0.36), $SpO_2 \geq 90\%$: -4 points

O2 administration route is via mask and reservoir bag: -5 points

O2 administration route is via high flow: -6 points

O2 administration route is via artificial ventilation management: -7 points

In the event of data that does not correspond to the scoring method above, refer to device changes and the oxygen dose before and after the time of data input to allocate an appropriate score. In such instances, leave a description of the score allocation.

Reference: Extract from the protocol (secondary endpoint: evaluation of changes in SpO_2)

$SpO_2 \geq 96\%$ in room air: 0 points

$93\% \leq SpO_2 < 96\%$ in room air: -1 point

$90\% \leq SpO_2 < 93\%$ in room air: 2 points

$SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 1–2 L: -3 points

$SpO_2 \geq 90\%$ maintained with the use of an oxygen cannula at 3–4 L/min: -4 points

Oxygen therapy with a mask, reservoir mask: -5 points

Noninvasive positive pressure ventilation, high flow nasal oxygen: -6 points

Artificial ventilation, ECMO: -7 points

4. Evaluation of scored pneumonia

For evaluations of pneumonia on chest CT measured according to 5 categories, the scores assigned as follows will be considered

Marked improvement: +2 points
Slight improvement: +1 point
No change: 0 points
Slight exacerbation: -3 points
Marked exacerbation: -5 points

5. The length of hospitalization and event indicator variable

The length of hospitalization will be defined as the period from the day of hospitalization until the day of discharge, the day of satisfying the discharge criteria, or death, whichever is earliest. The event indicator variable will be created as follows.

When the outcome is hospitalization at one's own institution at the time point the observation completion or discharge (hospital transfer): 0 (censored)
When the outcome is discharge: 1 (with event)
When the outcome is death: 2 (censored or competing event)

Furthermore, analysis items considered to be censored or competing events at the time point of exacerbation will be included. Patients who discontinue the investigational treatment and switch to standard treatment as well as patients admitted to the ICU will be defined as patients with exacerbation. The extraction criteria include patients "with comment" under "other" for the discontinuation reason and those who are in the ICU.

6. The timing of adverse event onset

The time of onset of adverse events (n^{th} day of treatment) will be calculated as "the day of adverse event onset − the treatment starting date +1."

7. Subset analysis

For complications and comorbidities, data collection items and associated treatments are defined as follows.

(Diabetes mellitus data will be collected from the "comorbidities" form below)

Hypertension: On the "Admission Signs and Symptoms" form, Systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg
Diabetes mellitus: mild diabetes mellitus and severe diabetes mellitus
Cardiovascular illness: Myocardial infarction, congestive heart failure, and peripheral vascular disease

(Including intermittent claudication, bypass surgery, gangrene, and untreated thoracoabdominal aortic aneurysm)

Obesity: Obesity (based on the physician's diagnosis)

Chronic respiratory illness: Chronic lung disease (to the extent of causing difficulty breathing on slight exertion)

Bronchial asthma: (based on the physician's diagnosis)

Malignant tumor: Solid carcinoma (without clear metastasis over the last 5 years)

Leukemia: (including acute and chronic leukemia as well as polycythemia rubra vera)

Lymphoma: (including lymphosarcoma, macroglobulinemia, and myeloma)

Metastatic) solid carcinoma

7. Analysis set

7.1. Definition of set

1. Effectiveness analysis set (Intention-to-treat, ITT)

Study subjects who are enrolled in this study, randomly allocated to a group, given even a single dose of the investigational drug, and without major violation of protocol (such as consent not being obtained and enrolment outside of the enrolment period) will be defined as the effectiveness analysis set (ITT).

2. Per protocol set (PPS)

Study subjects among the ITT set, excluding those with a major violation to the protocol as outlined below, such as the study methods, and concomitant therapies, will be defined as the PPS.

- Inclusion criteria violation
- Exclusion criteria violation
- Violation of contraindicated drugs
- Violation of contraindicated therapies

3. Safety analysis set (SAS)

Study subjects who are given the investigational drug, even once, after allocation will be defined as the SAS.

7.2. Breakdown of subjects

Analysis set: all subjects

In each group, we will tabulate enrolled patients, allocated patients (eligible patients), noneligible patients, patients excluded from the SAS, patients included in the SAS, patients excluded from the ITT, patients included in the ITT, patients excluded from the PPA, and patients included in the PPS. The reason for ITT exclusion, SAS exclusion, and PPS exclusion will be tabulated in each group.

7.3. List of discontinued subjects during the study period

Analysis set: all patients

For patients who discontinue during the study period, the reason for discontinuation will be tabulated in each group. The patient identification code, sex, age, date of providing consent, discontinuation date, discontinuation management classified on the basis of the discontinuation reason, and other details/ doctor’s comments will be presented in a list.

Furthermore, the discontinuation reason will be classified as follows.

1) When it is deemed difficult to continue the study due to onset such as that of illness
2) When a subject can no longer be followed-up

3) When pregnancy or suspected pregnancy occurs
4) When a subject or their legal representative requests to withdraw participation from the study
5) Non-compliance in drug-taking
6) Violation of protocol
7) When contraindicated drugs must be administered or when they have been administered
8) When a caregiver who can cooperate in the study is no longer available
9) When, for other reasons, the principal investigator or subinvestigator judges continuation of the study to be difficult

8. Study population

8.1. Distribution of variables at baseline

Analysis sets: ITT, PPS, SAS

Baseline data based on section 6.1 will be processed, and the summary statistics will be calculated overall and for each group. In the category variables tabulation, missing data will be handled as 1 category, in which the number and ratio of patients will be calculated.

Regarding the patient background, summary statistics will be calculated for the following variables.

Age (years), age (≥50 or <50 years), sex (male or female), severity, number of days from the day of COVID-19 onset until the day of hospitalization (days), complications (presence or absence), presence or absence of pregnancy (yes, no, unclear), state of physical activity before hospitalization (Eastern cooperative Oncology Group performance status 0, 1, 2, 3, 4), presence or absence of smoking habit [current smoker (until immediately before onset), past smoker, no smoking history, and unclear], number of cigarettes per day (cigarettes), number of smoking years (years), smoking index (Brinkman index), weight (kg), body height (cm), travel to regions with a COVID-19 outbreak within 14 days of onset (yes, no, unclear), close contact with patients with confirmed or suspected COVID-19 within 14 days of onset (yes, no, unclear), presence or absence of comorbidity (each item from myocardial infarction to AIDS or HIV infection (item acquired on the EDC system, respectively), drug allergies (with, without, unclear), and medical history that should be mentioned (with, without, unclear).

Regarding vital signs, summary statistics will be calculated for the following variables.

Body temperature (℃) , systolic blood pressure (mmHg), diastolic blood pressure (mmHg)、heart rate (bpm), SpO_2 (%), respiratory rate breaths per minute, oxygen administration route (cannula, mask, reservoir bag, and high flow)

With regard to signs and symptoms at hospitalization, summary statistics will be calculated for the presence or absence of the following.

Fever (≥37.5℃), coughing, moisture, bloody sputum/ hemoptysis, pharyngalgia, nasal discharge, wheezing, difficulty breathing, chest pain, muscular pain, joint pain, headache, alteration of consciousness/confusion, sense of fatigue/malaise, abdominal pain, vomiting/ nausea, and diarrhea

On imaging procedures, the summary statistics of the following variables will be calculated.

Chest X-ray photo findings [no clear abnormality, features of pneumonia (including infiltrative shadow and interstitial shadow), and with abnormal shadow other than features of pneumonia]

Chest CT scan findings [no clear abnormality, features of pneumonia (including infiltrative shadow and interstitial shadow), and with abnormal shadow other than features of pneumonia]

For tests of respiratory illness, the summary statistics of the following variables will be calculated.

Implementation of rapid kit testing (yes, no), influenza (A-positive, B-positive, negative, not performed), RS virus (positive, negative, not performed), adenovirus (positive, negative, not performed), mycoplasma (positive, negative, not performed), streptococcal (positive, negative, not performed), human metapneumovirus (positive, negative, not performed)

For test findings, the summary statistics of the following variables will be calculated.

Albumin (Alb)(g/dL), lymphocyte count (%), CRP(mg/L), D-dimer (μg/mL), PIC (mg/dL), TAT (μg/mL), white blood cell count ($\times 10^3/\mu L$), thrombocyte count ($\times 10^3/\mu L$), bilirubin (mg/dL), AST(U/L), ALT(U/L), LDH(U/L), ALP(U/L), creatinine kinase (CK, CPK) (U/L), creatinine (mg/dL), BUN (mg/dL), sodium (Na) (mEq/L), potassium (K) (mEq/L), glucose (Glu) (mg/dL), uric acid (mg/dl), procalcitonin (ng/mL), hemoglobin (g/dL), hematocrit (%), neutrophil count (%), monocytes, eosinophils, basophils, APTT, PT-INR, γ-GTP (U/L), and erythrocyte sedimentation rate (mm/h)

8.2. Drug-taking status

Analysis set: ITT

The summary statistics of the presence or absence of avigan (favipiravir), foipan (camostat mesilate), alvesco (ciclesonide), other anti-SARS-Cov-2 drugs, other antiviral agents, antimicrobial agents, antifungal agents, and steroids were calculated according to each group and time point.

With regard to avigan (favipiravir), foipan (camostat mesilate), and alvesco (ciclesonide), the summary statistics were calculated for the presence or absence of changes in dose and administration method.

8.3. Examination of primary endpoints

Primary endpoint: length of hospitalization

1. Main analysis of the primary endpoints

Analysis set: ITT, PPS (ITT only in the subset analysis stipulated in section 8.6.8)

Regarding the length of hospitalization, survival curves will be created for each group using the Kaplan–Meier method, with which the non-discharged /discharged ratio as well as the median number of days of hospitalization will be calculated on days 7, 14, 21, and 28. To calculate the 95% CI non-discharged /discharged ratio, double logarithmic transformation will be used. To calculate the 95% CI for the median number of days of hospitalization, the Brookmeyer and Crowley method will be used.

The survival curve will be defined as 1-Kaplan–Meier curve and will describe the cumulative discharge ratio. Event indicator variables 0 and 2 will be treated as censoring. Patients with a length of hospitalization of >1 month (28 days) will be censored at 28 days. Furthermore, censoring of death will be considered as 28 days. An intergroup comparison will be conducted by stratified log-rank test with allocation factor [age (≥50 years, <50 years)], sex (male, female), severity (moderate I and moderate II), and complications (presence or absence) as stratum. Similarly, with the allocation factor as the covariate, the hazard ratio of the combination therapy group versus the monotherapy group will be calculated along with the associated 95% CI using Cox's proportional hazard model.

2. Secondary analysis of the primary endpoint

Analysis set: ITT

Instead of considering the length of hospitalization in the main analysis of the primary endpoint, we will perform the following: 1. an analysis of when using the period from the onset date to discharge and 2. a landmark analysis starting from day 2 and excluding patients who develop some kind of event (discharge, censoring, exacerbation, or death) up to day 2 of hospitalization. Furthermore, 2 landmark analyses, as 3 and 4, will be performed when changed to the day 3, and day 5.

A survival curve will be created for each group using the cumulative incidence function for the length of hospitalization, using which the non-discharged /discharged ratio on days 7, 14, 21, and 28 will be calculated (competing risk analysis). To calculate the 95% CI of the non-discharged/discharged ratio, the counting process method will be used. The event indicator variable 0 will be treated as censoring, and 2 (death) will be treated as a competing risk of discharge. Exacerbation will also be treated as a competing risk on the discontinuation day. An intergroup comparison will be performed by stratified Gray test, with allocation factor [age (≥50 years, <50 years)], sex (male, female), severity (moderate I, moderate II), and complications (presence or absence) as stratum. Similarly, with the allocation factor as the covariate, the sub-distribution hazard ratio of the combination therapy group versus the monotherapy group will be calculated along with the associated 95% CI using Fine and Gray's proportional hazard model.

For the competing risk analysis, instead of considering the length of hospitalization, we will perform 1. an analysis of when using the period from the onset date to discharge and 2. a landmark analysis starting from day 2 and excluding patients who develop some kind of event (discharge, censoring, exacerbation, or death) up to day 2 of hospitalization. Furthermore, 2 landmark analyses, as 3 and 4, will be performed when changed to the day 3 and day 5.

8.4. Examination of secondary endpoints

Analysis set: ITT

1. Changes in clinical findings on days 4, 8, 11, 15, and 29 after treatment: body temperature, oxygen usage status, respiratory rate, oxygen saturation, severity, presence or absence of artificial ventilator usage, ECMO usage, presence or absence of ICU management, and state of other concurrent drug usage.

Summary statistics of body temperature, respiratory rate, SpO_2, and severity will be calculated for each group and time point. At each time point, an intergroup comparison will be performed using a *t*-test (equal variance not assumed).

Summary statistics will be calculated for each group and time point for changes in body temperature, respiratory rate, and SpO_2 from baseline values. At each time point, an intergroup comparison of the amount of change from baseline will be performed using a *t*-test (equal variance not assumed).

Summary statistics will be calculated for each group and time point for the oxygen administration route (cannula, mask, reservoir bag, and high flow), severity, presence or absence of artificial ventilation, and presence or absence of ECMO. At each time point, an intergroup comparison will be performed using Fisher's exact probability test (presence or absence of artificial ventilation and presence or absence of ECMO usage) and chi-square test (oxygen administration route and severity).

For the presence or absence of ICU management, regarding the presence or absence of ICU management at least once during hospitalization, the summary statistics will be calculated according to each group, and an intergroup comparison will be performed using Fishers exact probability test.

Regarding the state of other concomitant drug usage, for the presence or absence of other antiviral agents, antimicrobials, antifungal agents, and steroids, the summary statistics will be calculated according to each group and time point, and an intergroup comparison will be performed using Fisher's test

2. Changes in test findings on days 4, 8, 11, 15, and 29 after treatment: Alb, lymphocyte count, CRP, D-dimer, PIC, TAT, white blood cell count, thrombocyte count, bilirubin, AST, ALT, LDH, ALP, CK, creatinine, BUN, Na, K, Glu, uric acid, procalcitonin

Summary statistics will be calculated for each group and time point for each test value. At each time point, an intergroup comparison will be performed using a *t*-test (equal variance not assumed).

Summary statistics will be calculated for each group and time point for changes in each test value from baseline. At each time point, an intergroup comparison of the amount of change from baseline will be performed using a *t*-test (equal variance not assumed).

3. SARS–CoV2 viral genome size on days 8, 15, and 29 after treatment

The summary statistics will be calculated according to each group and time point with regard to test

positivity and negativity. At each time point, an intergroup comparison will be performed for testing positivity and negativity using Fishers exact probability test.

The summary statistics of the viral genome size (copy/μL) will be calculated according to each group and time point. At each time point, an intergroup comparison of the viral genome size will be performed (copy/μL) using a *t*-test (equal variance not assumed). In the summary statistics, the power of the viral genome size calculation will be presented according to the data (such as 7.0×10^6). A *t*-test of the viral genome size will be performed of the value obtained following logarithmic transformation. When the viral genome size is below the detection limit (1×10^2 copy/μL), it will be included in the tabulation as detection limit/2.

4. The presence or absence of antibody production (IgM, and IgG) on days 8, 15, and 29 of treatment

The summary statistics will be calculated according to each group and time point with regard to the presence or absence (or unknown) of IgG antibody and IgM antibody production. At each time point, an intergroup comparison of the presence or absence of production will be performed using Fishers exact probability test.

8.5. Analysis of exploratory endpoints

1. Evaluation of scores severity, scored respiratory function, and scored pneumonia

The summary statistics will be calculated according to each group and time point with regard to each respective score. At each time point, an intergroup comparison will be performed using a *t*-test (equal variance not assumed).

Summary statistics will be calculated for each group and time point for the amount of change in scored respiratory function from baseline values. At each time point, an intergroup comparison of the amount of change from baseline will be performed using a *t*-test (equal variance not assumed).

8.6. Points for statistical analysis

1. Covariate adjustment

In the main analysis of the primary endpoints, a Cox proportional hazard model will be adjusted for the allocation factors.

2. Handling of omissions and missing data

Missing data will not be supplemented.

3. Interim analysis and monitoring

This does not apply to the present study.

4. Multicenter collaborative study

In the present study, an analysis considering the institutions will not be performed

5. Multiple comparisons and multiplicity

This does not apply to the present study.

6. Subset usage in the evaluation of effectiveness

The tabulation results of the ITT, PPS, and SAS will be presented in section 8.1.

7. Examination using an actual control drug to show equivalence

This does not apply to the present study.

8. Subset examination

Regarding the main analysis of the primary endpoint, subset analyses will be performed based on the following classification. In the subset analyses, variables prescribing a subset will be excluded from the analysis covariates.

・Severity (moderate I and II)

・Complications, and comorbidities (those with hypertension, diabetes mellitus, cardiovascular illness, obesity, chronic respiratory illness, and malignant tumor)

・Age (<65 years, ≥65 years <80 years, and ≥80 years)

9. Safety evaluation

The SAS will be analyzed.

As a rule, adverse events will be interpreted using the latest medical dictionary for regulatory activities (MedDRA) of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

9.1. Summary of adverse events

Analysis set: SAS

For all adverse events, all adverse reactions (adverse events in which a relationship cannot be excluded or judged to have a relationship), all serious adverse events, all serious adverse reactions, and adverse events that lead to death (among serious adverse events, those that lead to death), the number of cases, number of patients, and incidence (number of patients/number of patients in the SAS) will be presented for each group.

9.2. Evaluation of adverse events

Analysis set: SAS

1. Presentation of adverse events

Adverse events will be tabulated using the system–organ–class (SOC) and preferred term (PT). Furthermore, for the SOC, the primary SOC will be used.

For all adverse events, the number of cases, number of patients, and incidence (the number of patients/number of patients in the SAS) will be presented for each group. Furthermore, the maximum degree of each patient (mild, moderate, and severe), relationship (without relationship, a relationship cannot be excluded, and with relationship), and the number of patients with the ratio of serious adverse events will be tabulated.

For all adverse events, the number of cases, number of patients, and incidence will be calculated according to the SOC and PT.

The following items will be presented in a table. The table will be sorted in the order of group, patient identification code, and adverse event onset.

- Patient identification code
- Date of consent acquisition
- Event onset date
- Onset time (X day of treatment)
- Adverse event name
- SOC name
- PT name

- Degree (mild, moderate, and severe)
- Investigational drug treatment
- Causal relationship with the present study
- Adverse event outcome (recovery, remission, unrecovered, with sequelae, death, unable to follow-up)
- Seriousness (serious and non-serious)
- Details of seriousness

2. Presentation according to the degree of adverse events (mild, moderate, and severe)

The number of cases, number of patients, and incidence will be calculated according to group and degree (mild, moderate, and severe) (according to SOC, and PT).

3. Presentation of serious adverse events

For adverse events and adverse reactions judged to be serious (adverse events in which a relationship cannot be ruled out or judged to have a relationship), the number of cases, number of patients, and incidence will be calculated for each treatment group. Furthermore, the same items as in "2. Presentation of adverse events" will be presented in a table. The table will be sorted in the order of group, patient identification code, and adverse event onset.

10. Additional analysis of effectiveness

1. A diagram of the change in image evaluations of pneumonia

The ITT set will be used as the analysis set. Regarding evaluations of pneumonia based on chest X-ray compared with at hospitalization, a spaghetti plot will be created for each group (transition diagram for each individual). The same will be created for chest CT scans.

2. Analysis of primary endpoints using data obtained up to day 14

Most patients with exacerbation are discharged after 14 days, and therefore, even when discharged after day 14, the following analysis will be performed with day 14 treated as censoring. The purpose will be to perform exploratory evaluation of the drug efficacy without including the discharge of patients with exacerbation.

The ITT set will be the analysis set. For the length of hospitalization, a survival curve will be created for each group using the Kaplan–Meier method, using which the non-discharged/discharged ratio on days 7 and 14 as well as the median number of days of hospitalization will be calculated. Patients who are hospitalized after day 14, and deaths, the day of censoring will be treated as day 14. To calculate the 95% CI non-discharged /discharged ratio, double logarithmic transformation will be used. To calculate the 95% CI for the median number of days of hospitalization, the Brookmeyer and Crowley method will be used. The survival curve will be defined as 1-Kaplan–Meier curve and will describe the cumulative discharge ratio. Event indicator variables 0 and 2 will be treated as censoring. An intergroup comparison will be conducted using stratified log-rank test with allocation factor [age (≥50 years, <50 years)], sex (male, female), severity (moderate I, moderate II), and complications (presence or absence) as stratum. Similarly, with the allocation factor considered as the covariate, the hazard ratio of the combination therapy group versus the monotherapy group will be calculated along with the associated 95% CI using Cox's proportional hazard model.

3. Distribution of severity, including death, discharge, and discharge (transfer)

The distribution of severity, including death, discharge, and discharge (transfer), in all patients will be created on day 0, 4, 8, and 11. Missing data will be supplemented using the last observation carried forward method.

Supplementation using the last observation carried forward method:

In patients with exacerbation, the severity after exacerbation will be increased by 1 category above that of the preceding time point. When severe at the preceding time point, the severity will be supplemented.

4. Post-hoc subset analysis

The following subset analyses will be performed.

・BMI (cutoff value: 25/30, 22/27, 25)

・Age (cutoff value: 50/60/70, 50/65, 60)

・Smoking [with smoking history (current smoker and past smoker), never smoked]

・Combination of the age and BMI categories